Major depressive disorder (MDD) carries the largest burden of all diseases in middle and high income countries, as determined by the World Health Organization (2008). SSRIs are generally used as first-line treatment in the treatment of MDD. It is therefore imperative to understand their mechanism of action in order to improve the effectiveness of the treatment of MDD. Indeed, only about a third of patients with MDD will remit in a first trial with these agents (Trivedi et al., 2006).

It is well known that SSRIs rapidly inhibit the serotonin (5-hydroxytryptamine [5-HT]) transporters, within hours, and yet begin to exert an antidepressant response well after they achieve a steady-state level in the human brain. The increase in 5-HT transmission in forebrain areas, which should result from preventing the reuptake of 5-HT in presynaptic terminals, is likely dampened by a decrease in firing of 5-HT neurons because 5-HT reuptake is inhibited at their cell body level. This results in a marked dampening of behavioral action presumably resulted from the already dampened sensitivity of 5-HTT1A autoreceptors, not requiring the firing of 5-HT neurons to be silenced to produce a recovery to normal of the firing of 5-HT neurons in the presence of reuptake inhibition. This result is in a marked increase in 5-HT transmission in projecting areas because 5-HT release is highly dependent on firing. The desensitization of the 5-HTT1A autoreceptor thus corresponds in time with the onset of action of SSRIs in MDD.

Dr René Hen’s group reports herein extensive experiments to advance our knowledge on the role of this 5-HTT1A autoreceptor in the antidepressant-like response in mice (Richardson-Jones et al., 2010). Their contribution represents a landmark in this field for several reasons, emphasized in this Preview. First, they generated mice with a conditional suppression of the expression of 5-HTT1A autoreceptors in the raphe nuclei, without affecting the postsynaptic 5-HTT1A receptors in projecting areas of the 5-HT neurons. The engineering of these mice represents a major advancement above the production of constitutional null mutant mice for the 5-HTT1A receptor (Ramboz et al., 1998), since knockout mice do not allow for deciphering the role of this receptor in adulthood from that of changes that may have occurred during development in the absence of the receptor. Furthermore, the 5-HTT1A receptors are located both pre- and postsynaptically, where they exert opposite functions on overall 5-HTT1A transmission. Therefore, in constitutinal 5-HTT1A knockout mice, postsynaptic 5-HTT1A transmission is abolished whereas that at other 5-HT receptors may be enhanced due to increased 5-HT neuron function.

Although the density of 5-HTT1A autoreceptors in the raphe was decreased only by about 30% in their mice, the physiological impact was major. Overall, the average firing rate of 5-HT neurons in the dorsal raphe of these 1A-Low mice was double that of 1A-High mice. There was still an overlap in the firing rates in the two groups, likely resulting from about half the 5-HT neurons having lost their responsiveness to a 5-HT autoreceptor agonist in the 1A-Low mice and half retaining normal sensitivity. Behaviorally, the 1A-Low and 1A-High mice did not exhibit differential baseline anxiety in two conflict-based models. In contrast, after a few weeks of repeated stress, the 1A-Low mice displayed less behavioral despair in depression-related stress paradigms.

It is interesting to note that, although the significant differences between the groups of mice in these behavioral models were not large, they were of the same magnitude as the decreased expression of the 5-HTT1A autoreceptor. These 1A-High and 1A-Low mice may thus have clinical relevance for understanding the effects of the human polymorphism C(1019)G for the 5-HTT1A receptor (Lemond et al., 2003), where C carriers tentatively express lower 5-HTT1A autoreceptor levels than the G carriers. In order to address whether the antidepressant-like response to an SSRI could differ in mice with a differential expression of the 5-HTT1A autoreceptors, Hen’s group used the novelty suppression feeding test, which is sensitive to acute benzodiazepine administration, but only to prolonged use of antidepressant drugs (Merali et al., 2003). In this paradigm, the 1A-High mice did not respond to prolonged SSRI administration, but the 1A-Low presented an antidepressant-like response to the SSRI, after both an 8 day and a 26 day regimen. These results first suggest that this specific paradigm in this particular strain of mice may be conceived as a human equivalent to SSRI response (1A-Low) and resistance (1A-High). Second, they imply that the more rapid onset of behavioral action presumably resulted from the already dampened sensitivity of 5-HTT1A autoreceptors, not requiring...
prior desensitization before obtaining enhanced 5-HT transmission by the SSRI. This interpretation was supported by the greater enhancement of extrasympathetic 5-HT levels, measured using microdialysis in two depression-related brain structures, with an acute SSRI challenge in drug-naive 1A-Low mice when compared to 1A-High mice. The baseline levels of 5-HT were, however, identical at baseline. Furthermore, the levels of 5-HT were enhanced after only 8 days of SSRI administration in the 1A-Low mice, but not in the in the 1A-High mice. Nevertheless, 5-HT levels were similar after long-term SSRI administration in both groups of mice. This was consistent with the demonstrated capacity of the 5-HT1A autoreceptors to desensitize in the 1A-High mice.

In summary, this work by Hen’s group has permitted the examination of the 5-HT system by partially turning off the 5-HT1A autoreceptor at a specific point in time, allowing correlations to be made between alterations of 5-HT transmission and some antidepressant-like responses. While the study provides important new insights, there are also some caveats that should be considered more generally when using animal paradigms to mimic MDD in laboratory animals. Since many symptoms of MDD are subjective in nature and not always directly observable in patients, we can never be sure that the depressive syndrome is faithfully reproduced. An additional issue when using these models is which mouse strain would best represent the patient profile, since MDD is a heterogeneous condition in terms of symptoms presentation. For instance, the wild-type mice used in a prior Science paper from this group responded to prolonged administration of a SSRI (Santarelli et al., 2003), in contrast to a lack of response in the unaltered 1A-High mice strain. Nevertheless, the models used in this paper had sufficient face validity to test their hypothesis.

Finally, one has to additionally consider that there is likely a variety of altered neuronal elements that could contribute to the pathogenesis and/or the treatment response in MDD, even within the 5-HT system. For instance, beyond the 5-HT1A polymorphism, there is as well the polymorphism for the 5-HT transporter (Murphy et al., 2008). There may even be synergistic action between such neuronal elements in explaining SSRI response, or lack of, in depressed patients (Arias et al., 2005).

For the Future

The present paper leaves us with some open questions for future consideration. For instance, one would have expected a behavioral response after the long-term SSRI administration in the 1A-High mice given that 5-HT levels were enhanced to the same extent in the hippocampus and frontal cortex as in 1A-Low mice. While the authors initially postulated that 5-HT1A-mediated serotonergic tone prior to treatment is critical for establishing treatment response,” their later proposal of “subtler differences in serotonergic tone” is possibly a more likely explanation. Microdialysis assesses the extracellular levels of neurotransmitters which may not always reflect their synaptic concentrations. The synaptic release of 5-HT per electrical impulse is more under the control of the terminal 5-HT1B autoreceptor than that of the 5-HT transporter (Chaput et al., 1986). The 5-HT1B autoreceptor, which also desensitizes after prolonged SSRI administration (Pinheiro and Blier, 1999), may have downregulated its function to a greater extent in the 1-Low than in the 1-High mice.

Related to methodological issues is the assessment of the degree of desensitization of the 5-HT1A autoreceptor. Using the hypothermia response in mice, it appears that the desensitization was of the all or none fashion following SSRI administration. Using electrophysiological approaches, prolonged SSRI administration generally produces a 2- to 3-fold shift to the right of the dose-response curve to a cell body 5-HT autoreceptor agonist (Pinheiro and Blier, 1999). As mentioned by the authors, a different degree of 5-HT1A autoreceptor desensitization may well be present in SSRI-treated 1A-High and 1A-Low mice. The spontaneous firing rate of 5-HT neurons may thus be differentially affected by the long-term SSRI regimen in 1A-Low and 1A-High mice. The latter two parameters could be investigated using electrophysiological techniques.

In closing, the paper by Richard-Jones et al. has provided evidence for alterations in the function of 5-HT neurons in the presence of altered 5-HT1A autoreceptor expression. These findings may help us understand why G carriers of the 1029 5-HT1A polymorphism may not respond as well to serotonergic drugs (Lemone et al., 2004). Such research endeavors are also useful for better understanding the poor remission rates obtained with a first antidepressant medication and for providing support for optimizing therapeutic interventions on the basis of the heterogeneity of patients with regard to the function of their 5-HT and, eventually, other neurotransmitter systems.

REFERENCES


